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Reducing the Risk of Dementia

Efficacy of Long-Term Treatment of Hypertension

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Helen Petrovitch, MD; Lenore J. Launer, PhD

Background and Purpose—The efficacy of treating older persons for hypertension remains controversial. Although clinical trials suggest no short-term harm, or some benefits, there are little data on the effect on cognitive function of long-term antihypertensive treatment. We evaluated the risk of dementia and cognitive decline associated with duration of antihypertensive treatment.

Methods—Data are from the Honolulu Asia Aging Study on Japanese American men followed since 1965. The subjects included in this analysis were hypertensive from midlife and dementia-free in 1991 (mean age 76.7 years). In 1991, 1994 and 1997, global cognitive function was assessed with the Cognitive Abilities Screening Instrument (CASI) and dementia by a standardized examination using international criteria. The sample was grouped by treatment duration (never-treated hypertensives (NTH), <5 years, 5 to 12 years, >12 years). Normotensive subjects up to 1991 were included in the analysis as a control group.

Results—For each additional year of treatment there was a reduction in the risk of incident dementia (hazard ratio [HR]=0.94, 95% CI, 0.89 to 0.99). The risk for dementia in subjects with >12 years of treatment was lower compared to NTH (HR for dementia=0.40; 95% CI, 0.22 to 0.75 and for Alzheimer disease HR=0.35; 95% CI, 0.16 to 0.78) and was similar to the normotensives. Nondemented subjects with 5 to 12 years of treatment had lower yearly CASI decline compared to NTH.

Conclusions—Results suggest that in hypertensive men, the duration of the antihypertensive treatment is associated with a reduced risk for dementia and cognitive decline. (*Stroke*. 2006;37:1165-1170.)

Key Words: dementia ■ hypertension ■ treatment

The benefits of treating hypertension in the elderly, particularly for stroke, heart attack and heart failure prevention, are well established.¹ However, concerns about hypertension management in the very old remain a source of intense debate.² Recent reports indicate geriatric health care providers still have reservations treating very old patients.³ One important consideration is the possible adverse effects of blood pressure-lowering on cognitive function.⁴

Various studies have reported that high blood pressure at midlife may increase the risk for late-life cognitive impairment, white matter lesions, clinical dementia, and neuropathological markers of Alzheimer disease (AD).^{5,6,7,8} Several observational studies suggest that treatment of hypertension decreases the risk of dementia in the elderly.^{9,10}

Clinical trials, such as the Medical Research Council's (MRC) trial, the Systolic Hypertension in the Elderly Program (SHEP) trial, the Systolic Hypertension in Europe (Syst-Eur) trial and the Study of Cognition and Prognosis in the Elderly (SCOPE) trial, have reported no or beneficial effects of antihy-

pertensive treatment on cognitive function and dementia.¹¹⁻¹⁷ There are also several trials currently in progress to test this question.^{18,19} However, except for 1 study¹¹ the mean age of the subjects enrolled in published clinical trials is about 60 years.^{12,13} Further studies were conducted on specific patient populations and had relatively short treatment periods.

What cannot be examined in these trials is the question as to whether the putative positive effect on cognitive function continues with treatment through to old age, when the incidence of dementia increases exponentially. This is important to know when interpreting the results of these trials, in designing new ones, and in making treatment decisions in older subjects at risk for dementia. At present, these data can only come from long-term prospective studies. The Honolulu-Heart Program (HHP)/Honolulu-Asia Aging Study (HAAS) provided the opportunity to study the association between duration of treatment and the risk of dementia and cognitive decline. Here, we focused on elderly men who were hypertensive since middle age, an age when blood pressure tends to increase.

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Methods

The HHP is a prospective population-based study²⁰ of Japanese American men born between 1900 and 1919 and living on Oahu, Hawaii, at baseline. The baseline examination started in 1965 and was followed by 2 subsequent midlife examinations in 1968 to 1970, and 1971 to 1974. At the fourth examination in late-life (1991–1993), the cohort was assessed for cognitive function and dementia as a part of the HAAS. Subsequent follow-ups to identify incident cases of dementia were conducted in 1994 to 1996 and 1997 to 1999. At each examination, physical measurements, demographic and medical information were collected. The study was approved by the Institutional Review Boards of the Kuakini Medical Center and the Honolulu Department of Veterans Affairs. Informed consent was signed by the study participants or a family representative.

Cognitive Function and Dementia Assessment

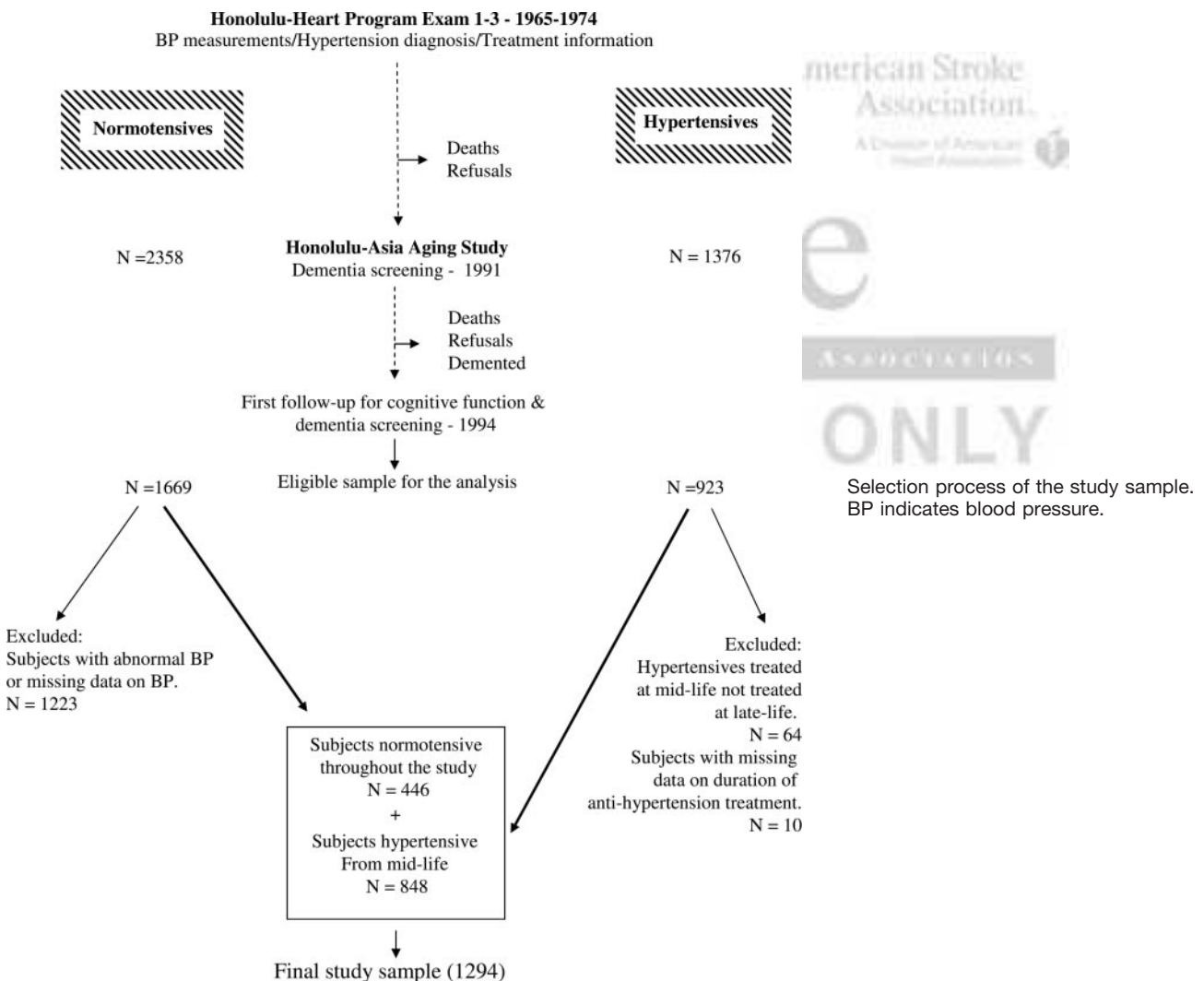
Assessment of cognitive function and screening for dementia have been described previously.^{21,22} Briefly, assessments were performed in 1991 to 1993, 1994 to 1996 and 1997 to 1999 (exams 4 to 6). At each examination, a participant's global cognitive status was evaluated with the 100-point Cognitive Abilities Screening Instrument (CASI),²³ a well-recognized instrument for the assessment of cognitive function in Japanese and Western sample populations.²⁴ A detailed dementia evaluation was conducted on screen positive men and included a proxy interview, detailed neuropsychologic assessment, neurologic examination and neuroimaging.²¹ A consensus committee reached a diagnosis using DSM-III R and DSM-IV

criteria for dementia,^{25,26} National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for AD,²⁷ and the California Alzheimer's Disease Diagnostic and Treatment Centers guidelines for vascular dementia (VaD).²⁸

Blood Pressure and Antihypertensive Treatment

As reported previously measurements of blood pressure (BP) were available from mid- and late-life examinations. Mean midlife blood pressure was the average of the mean values measured during the first 3 visits (1965–1974), and late-life blood pressure was the mean value from the fourth examination (1991–1993). History of hypertension and information on antihypertensive medication were self-reported by the subjects at the first 3 exams and required presentation of medication vials at the fourth examination. The question about duration of treatment was asked at examination 4 to those taking medication for hypertension. The Figure shows the selection process for the study sample. For the analysis, midlife hypertension was defined as self-reported hypertension ("Have you ever had high blood pressure or hypertension?") in at least 1 of the first 3 exams, or a systolic blood pressure (SBP) ≥ 160 mm Hg, or a diastolic blood pressure (DBP) ≥ 95 mm Hg, in agreement with blood pressure treatment guidelines in use at the time of midlife exams, or a report of taking antihypertensive medications.

Based on the midlife and late-life blood pressure and treatment history we created the following groups for the analysis: (1) midlife hypertensive never treated (n=142; 11.0%); (2) midlife hypertensive



treated (n=706; 54.8%). This group was further categorized based on late-life blood pressure into “controlled” (SBP <160 mm Hg and DBP <95 mm Hg; n=408) or “not controlled” by the fourth examination. The 706 treated hypertensives were grouped in roughly equal sized groups: treated for a maximum of 5 years before examination 4 (n=195; 15.0%), treated for at least 5 to 12 years before examination 4 (n=149; 11.5%), treated for >12 years before examination 4 (n=362; 28.0%). Further, we created a comparison group including subjects with normal blood pressure and no treatment throughout the study. To reduce the possibility that this group contained hypertensive subjects, we used more stringent criteria to define them, ie, SBP ≥140 mm Hg, or a DBP ≥90 mm Hg, in agreement with current recommendations (n=446; 34.5%).²⁹ Subjects that started the treatment after 1991 were not included in the analytical sample.

Covariate Measurements

The following covariates were included in the analyses: age; years of formal education; midlife body mass index (kg/m²) and smoking (pack/years of cigarette exposure); history of coronary heart disease and stroke assessed through a previously described surveillance system that was established in 1965. As an indicator of generalized atherosclerosis, we used the ankle-brachial index measured at the fourth examination and dichotomized with a cutoff of 0.9.³⁰ We also included *apolipoprotein E (APOE)* genotype determined by polymerase chain reaction amplification and restriction enzyme digestion.³¹ Subjects were categorized as *APOE ε4* positive if they had 1 or 2 copies of the *ε4* allele, and *ε4* negative otherwise.

Analytical Sample

The analysis is based on 1294 individuals of whom 108 were incident cases of dementia. Of these cases, 65 were classified as AD with and without cerebrovascular diseases, and 19 were diagnosed with VaD. The rest of the cases were classified as “other” types of dementia (n=24) and included Parkinson disease, dementia with Lewy bodies, Pick disease, alcoholism, head trauma, B₁₂ deficiency, hypothyroidism, progressive supranuclear palsy, and dementia of unknown causes. There was an average interval of 5.0 (1.6 SD) years between the time the question on duration of treatment was asked (examination 4) and the end of the follow-up.

Statistical Methods

Descriptive summaries of demographic and health-related characteristics from mid- and late-life were compared across the treatment groups using age-adjusted general linear models for continuous variables and age-adjusted logistic regression models for dichotomous outcomes.

Risk of Dementia

We compared the risk of dementia and dementia subtypes by treatment groups using discrete time survival analysis. This model is appropriate when event ascertainment occurs at examination cycles, rather than continuously. Dementia was counted as occurring sometime within the interval between the examination date the participant was dementia-free and the examination date when he was diagnosed as demented. Nondemented subjects who died during the follow-up time were included in the study up to their last examination. Age

TABLE 1. Characteristics of the HAAS Cohort by the Duration of Treatment With Antihypertensive Medication

	Treatment Duration of Midlife Hypertensives				Total	Normotensives
	Never	0–5	5–12	>12		
No.	142	195	149	362	848	446
Age at exam 4 (y)	76.9 (0.3)	77.2 (0.3)	77.3 (0.3)	76.7 (0.2)	77.0 (0.1)	76.3 (0.2)*
Age treatment started	...	74.7 (0.4)	68.3 (0.4)	54.6 (0.3)	63.0 (0.4)	...
Education (y)	10.9 (0.3)	10.7 (0.2)	10.9 (0.3)	10.8 (0.2)	10.8 (0.1)	10.9 (0.1)
Midlife						
BMI midlife (kg/m ²)	24.9 (0.2)	24.7 (0.2)	24.9 (0.2)	24.7 (0.1)	24.7 (0.09)	23.2 (0.1)†
Never smoked (%)	43.4	32.9	43.3	43.0	40.6	38.8
SBP midlife (mm Hg)	138.7 (1.2)	144.7 (0.9)†	146.0 (1.0)†	145.3 (0.7)†	144.2 (0.4)	115.8 (0.6)*†
DBP midlife (mm Hg)	88.2 (0.6)	91.4 (0.5)†	92.1 (0.6)†	90.8 (0.4)†	90.7 (0.3)	74.1 (0.4)*†
Late-life						
SBP at exam 4 (mm Hg)	154.7 (1.6)	157.3 (1.3)	152.2 (1.5)	159.3 (1.0)†	157.5 (0.6)	126.1 (0.9)†
DBP at exam 4 (mm Hg)	83.1 (0.9)	83.7 (0.8)	83.8 (0.9)	85.2 (0.6)	83.9 (0.3)	73.2 (0.4)*†
<i>APOE ε4</i> (%)	22.6	19.6	20.4	21.4	21.0	16.1‡
Prevalent disease						
ABI <0.9 (%)	10.5	14.3	11.1	11.6	11.9	5.8†
Prevalent Stroke (%)	1.4	5.6	3.3	3.6	3.6	1.8
Prevalent CHD (%)	18.3	12.8	9.4†	11.6†	12.6	6.5†*
Incident disease						
Dementia (%)	13.2	10.6	6.1¶	5.0†	7.8	6.9¶
AD (%)	9.0	4.4¶	3.8¶	2.7†	4.3	4.9¶
VaD (%)	3.1	5.2	0.01	1.1	2.3	0.0

Data are mean values (standard error) unless otherwise specified. *Age-adjusted *P* value <0.01 compared to the hypertensive group; †age-adjusted *P* value <0.01 compared to the hypertensive untreated group; ‡age-adjusted *P* value <0.05 compared to the hypertensive group; ¶age-adjusted *P* value <0.05 compared to the hypertensive untreated group. BMI indicates body mass index; ABI=ankle-brachial index; CHD=coronary heart disease.

squared at baseline was tested but found not significant. To determine whether late-life blood pressure levels in treated subjects modified the association, the analysis was stratified by whether or not the hypertension was "controlled" (SBP <160 mm Hg and DBP <95 mm Hg). To examine the possibility that signs of incipient cognitive decline led to a change in physician or participant behavior, or reporting of antihypertensive treatment, we repeated the analyses only among those with a CASI score above 82 at the baseline examination (n=1010).

Change in Cognitive Function

Changes in cognitive status between baseline, the second and third follow-ups were assessed by CASI (1991, 1994 and 1997). The association between the duration of treatment and cognitive decline in nondemented subjects (n=1186) was tested with a random effects model.³² Follow-up time was used as time scale. Subjects were censored at the date of the last follow-up examination they attended. The final model was adjusted for age and age-squared at the first cognitive function assessment and the same covariates that were included in the dementia models.

Bias Attributable to Loss to Follow-Up

We examined the bias attributable to selective loss to follow-up between midlife and the beginning of the dementia assessment by comparing groups defined by treatment status at midlife. Untreated and treated subjects had similar blood pressure at midlife (SBP=155.0 versus 155.1 mm Hg and DBP=91.4 versus 91.2 mm Hg, respectively). The loss to follow-up was higher in the untreated compared with treated hypertensives (66.8% versus 57.4%, probability value <0.001, adjusting for age, midlife SBP and DBP).

Results

Compared with normotensives, the hypertensive participants were older, had higher blood pressure values both at mid- and late-life, a higher BMI and lower ankle-brachial index, indicating more atherosclerosis. They also had a higher frequency of vascular disease and the *APOE* ϵ 4 allele (Table 1). Treated

hypertensives reported an average of 12.8 years (\pm 10.5 years) of treatment. Compared with the never-treated hypertensives, those who were treated had higher midlife SBP and DBP; subjects with at least 12 years of treatment had a higher late-life SBP and subjects with at least 5 years of treatment had a lower prevalence of coronary heart disease.

Each year of treatment was associated with a reduction of about 5% in the risk for dementia and subtypes (Table 2). As may be expected, those with 5 or less years of treatment were at similar risk for dementia as those never-treated hypertensives; those who eventually developed VaD were at even higher risk.

The association of treatment duration and dementia was modified by the success of the treatment. Those treated for 12 years or more had a similar risk for dementia compared with normotensives (odds ratio [OR]=0.82, 95% CI, 0.28 to 2.38). Subjects with controlled BP had significantly reduced the risk for dementia (OR=0.45, 95% CI, 0.22 to 0.91). When the analysis was restricted to those with an examination 4 CASI score higher than 82 (below this cut-off persons were identified as at risk for dementia), the results did not change in direction or significance (data not shown). The analysis stratified by BP control status in late-life showed that the effect of the duration of the antihypertensive medications was mainly among those with controlled BP levels (Table 3).

In nondemented participants, cognitive function declined with age. However, those with 5 to 12 years of treatment and those never hypertensive showed a lower cognitive decline over time compared with never-treated hypertensive subjects (Table 4). The results were similar, although the loss was greater, when subjects who became demented during the follow-up were included in the analysis (data not shown).

TABLE 2. Duration of Treatment With Antihypertensive Medication and Risk for Dementia, AD and VaD

	Dementia HR (95% CI)	AD HR (95% CI)	VaD HR (95% CI)
No.	1294	1251*	1205†
No. of cases	108	65	19
Duration of treatment (y)‡	0.94 (0.89–0.99)	0.96 (0.93–0.99)	0.94 (0.89–0.99)
Stratified by duration of treatment			
Never-treated hypertensives	1.00	1.00	1.00
Duration of treatment			
0–5 y	0.94 (0.52–1.72)	0.62 (0.27–1.43)	2.04 (0.6–6.9)
5–12 y	0.52 (0.24–1.09)	0.54 (0.21–1.36)	0.18 (0.10–1.71)
>12 y	0.40 (0.22–0.75)	0.35 (0.16–0.78)	0.32 (0.10–1.34)
Trend <i>P</i> value	0.001	0.014	0.009
Untreated normotensive	0.42 (0.20–0.89)	0.26 (0.10–0.66)	NA¶
Controlled BP§	0.45 (0.22–0.91)	0.24 (0.10–0.63)	0.42 (0.10–1.96)

Results represent hazard ratio (95% CI) for dementia compared to the hypertensive nontreated group. The analyses were adjusted for age at baseline, education, *APOE* ϵ 4 status, midlife (mean of exam 1, 2 and 3) and late-life (exam 4) blood pressure, smoking status, body mass index, ankle-brachial index and coronary heart disease. *P* values are for tests of linear trend across the hypertensive groups. *The analysis did not include subjects with VaD (n=19). †The analysis did not include subjects with AD (n=65). ‡Analysis performed among hypertensive subjects only (n=848 for total dementia, n=814 for AD, and n=791 for VaD). NA indicates not available (no cases of VaD). ¶No cases of VaD are present in the untreated normotensive group. §Blood pressure controlled status was included as additional variable in the analysis with stratified duration of treatment.

TABLE 3. Duration of Treatment With Antihypertensive Medication and Risk for Dementia, Stratified by Late-Life BP Control Status

	Controlled BP	Noncontrolled BP
No.	408	440
	HR (95% CI)	HR (95% CI)
Duration of treatment (y)	0.95 (0.92–0.98)	0.97 (0.94–1.01)
Stratified by duration of treatment		
Never-treated hypertensives	1.00	1.00
Duration of treatment		
0–5 y	1.03 (0.47–2.28)	0.99 (0.37–2.63)
5–12 y	0.40 (0.14–1.00)	0.82 (0.26–2.49)
>12 y	0.33 (0.14–0.75)	0.55 (0.21–1.50)

Results represent hazard ratio (95% CI) for dementia compared to the hypertensive nontreated group. The analyses were adjusted for age at baseline, education, APOE ε4 status, midlife (mean of exam 1, 2 and 3) and late-life (exam 4) blood pressure, smoking status, body mass index, ankle-brachial index and coronary heart disease.

Discussion

Using data from a large cohort of prospectively followed Japanese American elderly men, we found the longer the duration of antihypertensive medication use, the significantly lower the risk for dementia. Our data also suggest that long-term antihypertensive treatment could slow the rate of cognitive decline in nondemented subjects.

Sixty percent of the subjects with a stroke or a transient ischemic event occurred within the past 5 years started an antihypertensive treatment after the event (data not shown). In this case the use of antihypertensive medications would not protect the brain from the damage caused by the stroke, which might explain the lack of effect in those treated for a relatively short time.

The observational data based on this study are consistent with a long-term benefit of antihypertensive treatment on brain pathology. In the context of these observational data, the relationship can reflect several mechanisms. First, they may reflect a direct BP-lowering effect; this is supported by the finding that duration of treatment was particularly beneficial in well controlled hypertensives in a dose-dependent manner. Long-term hypertension can damage large and small

TABLE 4. Duration of Treatment With Antihypertensive Medications and Yearly Cognitive Function

	Midlife Hypertensives' Treatment History				Normotensives
	Never	Years			
		0–5	5–12	>12	
No.	121	171	138	342	414
Initial CASI score	83.05	82.86	82.56	83.03	81.58
CASI change/y	-1.46*‡	-1.22	-1.14†	-1.08	-1.01†

The untreated hypertensive group is the reference group for the analysis. *P value <0.01 compared to a slope=0; †P value <0.05 compared to the reference group. The analysis was adjusted for age and age squared at baseline, education, APOE ε4 status, midlife (mean of exam 1, 2 and 3) and late-life (exam 4) blood pressure and smoking status.

vessels of the brain as well as act directly on neurons.³² An autopsy study on a subsample of this cohort showed a higher level of vascular lesions and neuritic plaques associated with elevated levels of BP.³³ Experimental and epidemiologic studies suggest a role of vascular disease in the pathology of AD.³⁴ Second, there may be some unmeasured characteristics of these well controlled hypertensives that we did not account for and that reduce the risk for dementia. Finally, attributable to deaths between the mid- and late-life exams, there is likely a selection bias toward hypertensives that were less severe or developed hypertension at a later date. This hypertension may have a different pathophysiologic basis that interacts with treatment.

Specific aspects of treatment, which may affect these analyses, cannot be evaluated with these data. These include the effects of particular drugs, indications for treatment with antihypertensive medications, and compliance to treatment. These factors have likely changed since the inception of the cohort.

We could have missed certain groups that had a different risk for dementia or treatment pattern than those included in the analysis. For instance, we may have missed those who started the treatment after midlife and stopped before the fourth examination, as well as those whom become demented and were lost to follow-up before the fourth examination. We observed a greater loss of follow-up from midlife to the fourth examination of untreated hypertensive subjects compared with those treated from midlife; this selective survival could have further reduced the evidence for the beneficial effect of antihypertensive treatment on dementia.

Ideally, the hypothesis that increased duration of treatment reduces the risk for dementia and cognitive decline needs to be tested in the context of a randomized trial.³⁵ Previous trials have yielded contradictory results regarding the efficacy of antihypertensive medication in preventing dementia. The trials were planned for relatively short times. These data suggest that a trial would need to be planned for a longer time. However, such trials will be increasingly difficult to mount because antihypertensive treatment is becoming more prevalent and is effective in reducing the risk for cardiovascular and cerebrovascular morbidity and mortality.^{1,36} These trends make placebo arms less possible to incorporate in a trial. Alternative designs will need to be considered.

In summary, our results suggest that initiation of antihypertensive treatment in long-term hypertensive older men may still provide the benefit of reducing cognitive decline and dementia.

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